REMARKS

The Amendments

Claims 32, 44 and 55 have been amended to address the Examiner's rejections in the Office Action.

The amendments to claim 44 are supported by e.g. the specification at page 6, lines 16-18 and original claim 31.

No new matter is added in any of the above amendments. The amendments are made in response to the Examiner's rejections in the Office Action. Applicants believe that the amendments address the Examiner's rejections and place the claims in a form for allowance.

The Response

35 U.S.C. §112 First Paragraph Rejection

The Examiner has rejected claims 32-33, 37, 41-47 and 52-57 under 35 U.S.C. §112, first paragraph, for not reasonably providing enablement for a method of detecting colorectal or breast cancer by determining the expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO:2. The Examiner acknowledges, however, that the specification is "enabling for a method of determining the predisposition of an individual to colorectal cancer by determining the expression of a nucleic acid that encodes an amino acid sequence of SEQ ID NO:2." (See Office Action at page 2). Applicants have carefully reviewed the Examiner's reasons for rejection and believe that the current amendments to claims 32, 44 and 55 fully remedy them.

As a preliminary matter, Applicants wish to point out that the claims as previously presented recite a "method of _detecting_" rather than "method of _diagnosing._" In the present Office Action, however, the Examiner characterized the scope of the claims as "broadly drawn to a method of _diagnosing_ breast cancer or colorectal cancer." (See, Office Action dated Dec. 24, 2003 at page 3). Applicants believe that one of ordinary skill in the art at the time of filing of the present application would recognize a method of _detecting_ breast or colorectal cancer as not requiring 100% accuracy. To the extent the Examiner has based her § 112 rejection on a

misinterpretation of the scope of the claims as requiring 100% accuracy, we assert that the rejection is improper and request that it be withdrawn.

Applicants have amended claims 32, 44 and 55 to recite "may indicate colorectal cancer" and "may indicate breast cancer." By amending the claims to recite "may indicate" Applicants have attempted to clarify further the sensitivity level and operability of the claimed methods for detecting colorectal or breast cancer.

In view of the foregoing clarification and amendments to the claims, Applicants assert that the specification teaches one of ordinary skill how to make and use the full scope of the claimed methods. The specification discloses a specific gene, CHA4 and its full length nucleic acid and amino acid sequences. The specification discloses gene expression data from actual DNA array experiments on 66 breast cancer samples, 77 colorectal cancer samples, 7 normal breast tissue samples, 4 normal colon tissue samples, and additionally dozens of other normal samples from the whole human "atlas" of body tissues. Each of these DNA array experiments is a working exemplification of one embodiment of the method of claims 32 and 52. Additional embodiments for measuring CHA4 expression are also disclosed in the specification e.g. RT-PCR, Northern analysis and RNase protection, or were well-known in the art.

The Examiner's official action cites two main reasons for rejection of the claims:

(1) Because the range of expression levels of CHA4 in breast cancer and colorectal tumors <u>overlaps</u> the range of expression levels in the corresponding normal breast and colorectal tissues, the use of CHA4 expression levels as a method of detecting breast or colorectal cancer is inoperable.

(2) Because the expression level data in the specification reflects hybridization to one specific oligonucleotide complimentary to a sub-sequence from the complete CHA4 nucleic acid sequence, the use of other variant or degenerate CHA4 nucleic acid sub-sequences to monitor CHA4 expression levels would require undue experimentation.

Applicants respectfully disagree with the Examiner's reasons for rejection and assert that

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the specification, together with the knowledge of one of ordinary skill in the art as of the filing date, teaches one of ordinary skill to practice the full scope of the claims with nothing more than routine experimentation.

With respect to reason (1), the Examiner has stated that the asserted overlap between the ranges of the breast cancer and normal tissue expression levels leads her to conclude that there "does not appear to be differential expression between the breast cancer tissues of Figure 3A and the 7 breast normal tissues." Applicants respond to this argument by pointing out that 65% of the breast cancer tissue samples, shown in Figure 3A, show elevated levels relative to the average CHA4 expression level observed in normal breast cancer tissue samples shown in Figure 3C. Applicants contend that one of ordinary skill in the art of breast cancer diagnostics at the time of filing of the instant application would view this data and conclude that CHA4 exhibits differential expression in breast cancer tissue relative to normal tissue. Applicants note that the Examiner has not provided any evidence that one of ordinary skill would reasonably view Applicants disclosure of 65% elevated levels as indicating absence of differential expression.

The Examiner has also concluded that "the specification teaches the overlapping ranges of normal and cancer expression of SEQ ID NO:1, therefore the skilled artisan would be required to perform additional experimentation to practice the invention as claimed." (OA at page 9). The Examiner, however, has not presented any findings of fact that support her conclusion that overlapping ranges are a problem, and that this problem requires more than routine experimentation to solve. Applicants wish to point out that the overlapping ranges of mRNA expression in cancerous versus normal tissues that the Examiner finds problematic also are observed for the well-recognized breast cancer biomarker, HER2. Applicants believe that the overlapping ranges for CHA4 (and HER2), while possibly affecting the commercial viability of a diagnostic device based on these targets, clearly do not rise to the level of non-enabling for the claimed methods of detecting breast cancer.

The Examiner also contends that "there is no indication in the specification of a threshold

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which would be indicative of colon or breast cancer tissue. Therefore, distinguishing a cancerous tissue from a normal tissue based solely on different sample expression would be unpredictable." (See Office Action at page 5). The Examiner concludes that further research and experimentation would be required that would be both unpredictable and undue. Once again, however, the Examiner has not presented any findings of fact that support her conclusion that the lack of a specified threshold is a problem requiring more than routine experimentation to solve. In fact, Applicants assert that one of ordinary skill would immediately recognize Figure 3 as disclosing a specific threshold that would enable the full scope of the claimed method. One of ordinary skill could simply determine the average value of the seven individual normal breast tissue samples in Figure 3C to be ~220 and use this as the threshold. Using this threshold, one of ordinary skill would detect breast cancer in 65% of the samples in Figure 3A. Once again, while it may be possible to further optimize various aspects of tissue sampling or other aspects of the method taught by the instant application and make a more commercially viable detection method based on CHA4, such optimal performance is not required by the claims. Moreover, it is well-accepted patent law that § 112 does not require one to teach a commercially viable invention. Accordingly, for the foregoing reasons, Applicants respectfully assert that the present disclosure which, exemplifies the detection of elevated expression of CHA4 in both breast and colorectal cancer samples relative to the average threshold expression values exhibited by normal tissues, fully complies with the enablement requirement of § 112 ¶1.

With respect to the Examiner's reason for rejection (2), the Applicants assert that the Examiner has set up a standard for enablement beyond that required by § 112 ¶1. Applicants have disclosed the full length nucleotide and amino acid sequences of the CHA4 gene. Furthermore, using a DNA microarray where the CHA4 gene represented by a unique oligonucleotide,T32108, Applicants have demonstrated that CHA4 gene is transcribed at elevated levels in breast and colorectal cancer tissues. Applicants assert that with these teachings one of ordinary skill could measure the expression of any nucleic acid sequence known to

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represent the CHA4 amino acid sequence in the context of the claimed method. The Examiner has speculated that "splice variants, SNPs, mutations, deletions, insertions," may exist that "may have different diagnostic implications on the nucleic acids." (see Office Action at page 6) The Examiner has also stated that the disclosure includes "no indication that all of the degenerate nucleic acids sequences encoding SEQ ID NO: 2 would have the same diagnostics as T32108." The Examiner, however, has not asserted any facts supporting the existence of any such problems, or any reason why such problems could not be overcome with anything beyond routine experimentation by one of ordinary skill in the art. For example, the problem of non-specific hybridization noted by the Examiner, has been known for years and routine methods for dealing with this problem are well-known to those of skill in the art. Applicants' specification recites well-known reference works and discusses methods for improving hybridization specificity at e.g. page 16, lines 10- page 17, line 7. Thus, the Examiner has not provided anything beyond speculation that the existence of sequence variants would prevent one of ordinary skill from using the claimed methods with anything more than routine experimentation.

With respect to Claims 44-47, the Examiner states that the specification allegedly does not teach how expression of SEQ ID NO:1 is predictive of prognosis. Applicants have amended Claim 44 to recite that wherein the expression of the gene at different cellular states is used to determine the prognosis of the individual.

Therefore, Applicants respectfully request that in view of the amendments of the claims and the above answers to the Examiner's reasons for rejection, the § 112, first paragraph rejection of Claims 32, 33, 37 and 41-47 should be withdrawn.

CONCLUSION

Applicants believe that the application is in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 463-8133.

Respectfully submitted,

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